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The Maternal Lifestyle Study: Effects of Substance Exposure During Pregnancy on Neurodevelopmental Outcome in 1-Month-Old Infants

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ABSTRACT. *Objective.* This was a prospective longitudinal multisite study of the effects of prenatal cocaine and/or opiate exposure on neurodevelopmental outcome in term and preterm infants at 1 month of age.

Methods. The sample included 658 exposed and 730 comparison infants matched on race, gender, and gestational age (11.7% born <33 weeks' gestational age). Mothers were recruited at 4 urban university-based centers and were mostly black and on public assistance. Exposure was determined by meconium assay and self-report with alcohol, marijuana, and tobacco present in both groups. At 1 month corrected age, infants were tested by masked examiners with the NICU Network Neurobehavioral Scale and acoustical cry analysis. Exposed and comparison groups were compared adjusting for covariates (alcohol, marijuana, tobacco, birth weight, social class, and site). Separate analyses were conducted for level of cocaine exposure.

Results. On the NICU Network Neurobehavioral Scale, cocaine exposure was related to lower arousal, poorer quality of movement and self-regulation, higher excitability, more hypertonia, and more nonoptimal reflexes with most effects maintained after adjustment for covariates. Some effects were associated with heavy cocaine exposure, and effects were also found for opiates, alcohol, marijuana, and birth weight. Acoustic cry characteristics that reflect reactivity, respiratory, and neural control of the cry sound were also compromised by prenatal drug exposure, including cocaine, opiates, alcohol, and marijuana and by birth weight. Fewer cry effects remained after adjustment for covariates.

Conclusions. Cocaine effects are subtle and can be detected when studied in the context of polydrug use and level of cocaine exposure. Effects of other drugs even at low thresholds can also be observed in the context of a polydrug model. The ability to detect these drug effects

requires a large sample and neurobehavioral tests that are differentially sensitive to drug effects. Long-term follow-up is necessary to determine whether these differences develop into clinically significant deficits. *Pediatrics* 2002;110:1182–1192; *infants, cocaine, opiates, polydrug use, pregnancy substance abuse, prenatal drug exposure, neurobehavior, NICU Network Neurobehavioral Scale, cry, multisite, heavy exposure, threshold effects, low birth weight, meconium.*

ABBREVIATIONS. MLS, Maternal Lifestyle Study; NICHD, National Institute of Child Health and Human Development; NIDA, National Institute on Drug Abuse; MISU, Maternal Interview of Substance Use; NNNS, NICU Network Neurobehavioral Scale; NBAS, Neonatal Behavioral Assessment Scale; ANOVA, analysis of variance; SES, socioeconomic status.

Substance abuse is a major public health problem that affects millions of children and places enormous financial and social burdens on society. Eleven percent of children (8.3 million) live with at least 1 parent who is either alcoholic or in need of treatment for the abuse of illicit drugs.¹ Of these, 3.8 million live with a parent who is alcoholic, 2.1 million live with a parent whose primary problem is with illicit drugs, and 2.4 million live with a parent who abuses alcohol and illicit drugs in combination.¹ Furthermore, substance use by pregnant women continues to be a serious problem.² The most recent report from the National Household Survey on Drug Abuse estimated that in 1999, the rate of drug use among pregnant women was 3.4% for illicit drugs, 17.6% for tobacco and 13.8% for alcohol.³ In the United States in 1999, there were 3 944 450 births to women aged 15 to 44 years.⁴ Using National Household Survey on Drug Abuse estimates of substance use during pregnancy, the approximate numbers of births in 1999 complicated by maternal use of illicit drugs, tobacco, and alcohol were 134 110, 694 220, and 544 330, respectively. Thus, from the public health perspective, the impact of substance use during pregnancy extends far beyond maternal health to that of a large number of the unborn population.

It is now well-documented that early scientific reports in the 1980s that portrayed children who were exposed to cocaine in utero as irreparably damaged were inaccurate.^{5–8} The 1990s brought concern with overinterpretation of the findings^{9,10} coupled with the recognition of methodological problems in published studies that limited our understanding of co-

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caine effects.^{7,11,12} Current research suggests that, although there are effects of cocaine on child development, these effects are inconsistent and subtle and need to be understood in the context of polydrug use and the caregiving environment.^{6–8,13–23} However, even subtle effects can affect substantial numbers of school-age children at an annual estimated cost to society of upwards of \$350 million for additional special education services for these children.²⁴

The Maternal Lifestyle Study (MLS) was developed in the early 1990s against the backdrop of debate and controversy about the effects of prenatal cocaine exposure on child outcome.^{25–27} The MLS is an interagency collaborative effort involving the National Institute of Child Health and Human Development (NICHD); the National Institute on Drug Abuse (NIDA); the Administration on Children, Youth and Families; and the Center for Substance Abuse Treatment. The MLS is the largest clinical prospective longitudinal study of acute neonatal events and long-term health and developmental outcomes associated with cocaine use during pregnancy. The MLS was developed with the recognition that cocaine use by pregnant women is a marker variable for 2 critical factors that can affect child outcome in addition to prenatal cocaine exposure: use of drugs other than cocaine and an inadequate caregiving environment. The MLS was designed to address many of the methodological issues in the field. They include, in addition to polydrug use and the role of the caregiving environment, sample size, methods of drug detection, prematurity, other confounding variables (eg, medical factors, interventions, protective services), and neurodevelopmental assessments that are sensitive to putative drug effects.

In this report, we present the first neurobehavioral findings from the MLS. We describe the effects of cocaine/opiate exposure on neurobehavioral outcome at 1 month of age in a large sample that was diverse with respect to geography, setting (urban/rural), race, and social class. The study used measures in neurobehavioral domains of neurologic integrity, behavior, stress/abstinence signs, and cry, which were selected for their sensitivity to cocaine effects. Drug exposure in all subjects was documented with meconium assay and self-report, preterm as well as term infants were included, and other confounding variables were controlled. We also conducted analyses to determine thresholds for cocaine effects and for the effects of other drugs.

METHODS

Study Design

The MLS was conducted at 4 NICHD Neonatal Research Network sites (Brown University, University of Miami, Wayne State University, and the University of Tennessee at Memphis). The study was approved by the institutional review board at each site. The study was conducted in 2 phases, acute outcome (phase I) and longitudinal outcome (phase II). After a summary of phase I,²⁷ we present the first neurodevelopmental findings from phase II.

Phase I was conducted between May 1993 and May 1995. During phase I, 19 079 mother-infant dyads were screened. Maternal exclusion criteria were age <18 years, identified psychosis or history of institutionalization for retardation or emotional prob-

lems, or language barriers that prevented her from giving informed consent or understanding the study. Infant exclusion criteria were outborn birth (not born at one of the participating hospitals), multiple gestation, birth weight <501 g, gestational age >42 weeks, or if in the judgment of the attending physician the infant was unlikely to survive. A NIDA Certificate of Confidentiality was obtained by each site that assured confidentiality of information regarding the subjects' drug use. The certificate superseded the mandatory reporting of illegal substance use that was in effect in the Florida and Rhode Island sites. The certificate was explained to the mother during the recruitment and informed consent procedure, including the condition that the certificate did not exclude reporting of evidence of child abuse or neglect. After informed consent was obtained, a maternal interview determined past and current drug use and sociodemographic information. A physical examination of the infant was conducted, and the infant's meconium was collected. Before mothers and infants were discharged, their charts were abstracted to collect selected medical data. Of the 19 079 subjects screened, 16 988 met the eligibility criteria and 11 811 mothers consented to participate in the study.

Meconium samples were collected in the nursery and shipped to a central laboratory (ElSohly Laboratories, Inc, Oxford, MS) for analysis of metabolites of illicit drugs (see ElSohly et al²⁸ and Lester et al²⁹ for details). The assay consisted of an enzyme-multiplied immunoassay technique screen for cocaine, opiates, tetrahydrocannabinol, amphetamines, and phencyclidine followed by gas chromatography/mass spectroscopy confirmation for presumptive positive screens.

The study definition of "exposure" was maternal admission of cocaine or opiate use during this pregnancy based on the hospital interview or positive gas chromatography/mass spectroscopy confirmation of cocaine or opiate metabolites. Although our primary interest was in cocaine, opiates were included in the exposed group because of hospital reports indicating that many cocaine users were also using opiates. "Unexposed" was defined as denial of cocaine or opiate use during this pregnancy and a negative enzyme-multiplied immunoassay technique screen for cocaine and opiate metabolites. A history of maternal alcohol, marijuana, and nicotine use during the pregnancy was recorded during the hospital interview and considered as background variables in both the exposed and unexposed groups.

Participants

The phase II longitudinal study began at the infant's first follow-up visit at 1 month (age corrected for prematurity). Mothers signed a separate consent for phase II. Infants were excluded from phase II when they had a chromosomal abnormality or TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis) infection confirmed before the 1-month visit or when the mother planned to move out of the catchment area. A list of possible comparison infants from the unexposed group within each center that matched an infant in the exposed group on race, gender, and gestational age was sent by the data center to each study site. Mothers were called on the list in sequence to confirm consent for phase II and to schedule the 1-month visit. When an infant in the comparison group did not attend the 1-month visit, another match was generated for each exposed infant until a comparison infant was successfully enrolled in phase II or the recruitment period ended. Recruitment of all exposed infants was attempted. It was possible for either an exposed or comparison infant to be in the study without a match. This procedure resulted in 2 groups that were matched on race, gender, and gestational age. The 1388 mother-infant dyads (658 in the exposed group and 730 in the comparison group) who came to the 1-month visit were enrolled in the longitudinal study.

The 1-month visit included neurobehavioral, medical, and physical status measures of the infant; social and demographic questionnaires; and the Maternal Interview of Substance Use (MISU). The MISU provides information about the frequency and quantity of substance use for each trimester during this pregnancy and was administered only to the biological mothers who brought their infant to the 1-month visit. The MISU was completed by 1255 biological mothers who brought their infants to the 1-month visit within the 2-week time frame, and the neurobehavior examination was completed on 1211 of those infants, which is the final sample in this study. Analyses of heavy cocaine effects ($n = 1032$) excluded opiate users ($n = 91$) and mothers who were identified as

using cocaine by initial hospital interview or meconium but denied use on the MISU ($n = 88$).

Measures

A neurodevelopmental assessment battery was specifically designed for this study through 3 years of age based on hypothesized mechanisms of action of the effects of cocaine on the “four A’s of infant behavior”: arousal, attention, affect (including social interaction), and action (motor patterning).^{8,30} All infants were examined between 42 and 44 weeks postconceptional age by trained personnel who were masked to infant exposure status. In this report, we present results of 1-month neurodevelopmental findings on 2 measures: the NICU Network Neurobehavioral Scale (NNNS)³¹ and acoustic cry analysis.

NNNS

The NNNS was administered by psychometrists who were certified on the examination. The NNNS was developed for the MLS and has been used in studies of intrauterine exposure to cocaine,³² opiates,^{33,34} and nicotine.³⁵ The NNNS provides an assessment of neurologic, behavioral, and stress/abstinence neurobehavioral function. The neurologic component includes active and passive tone, primitive reflexes, and items that reflect the integrity of the central nervous system and maturity of the infant. The behavior component is based on items from the Neonatal Behavioral Assessment Scale (NBAS)³⁶ modified to be sensitive to putative drug effects. The stress/abstinence component is a checklist of “yes” or “no” items organized by organ system based primarily on the work of Finnegan.³⁷ The NNNS follows a relatively invariant sequence of administration that starts with a pre-examination observation, followed by the neurologic and behavioral components. The stress/abstinence scale is based on signs observed throughout the examination. The NNNS items are summarized into the following scales: Habituation, Attention, Arousal, Regulation, Number of Handling Procedures, Quality of Movement, Excitability, Lethargy, Number of Nonoptimal Reflexes, Number of Asymmetric Reflexes, Hypertonicity, Hypotonicity, and Stress/Abstinence. Psychometric properties of the summary scales were evaluated with coefficient α and ranged from 0.56 to 0.85. The habituation data were not used, as most infants were awake at the beginning of the examination. The actual sequence of administration and the means used by the examiner to maintain an infant’s participation in the examination are recorded.

Cry Analysis

After completion of the NNNS, the infant was placed in the isolette and maintained in a noncrying state for 30 seconds before the cry was elicited. A Marantz PMD201 cassette recorder and Radio Shack Dynamic Unidirectional Microphone were used to record the cry for 30 seconds after stimulation to the sole of the infant’s right foot. If the infant did not cry, then a second stimulus was applied. The infant was supine with the microphone suspended 5 inches above the infant’s mouth. A specially designed stimulator and tone box automatically placed a tone on the tape to coincide with the time of the cry stimulus. A computer system used in other studies^{38–41} was designed specifically to perform the cry analysis (Cry Research Inc, Brookline, MA). Each 30-second cry signal was filtered above 5 kHz and digitized at 10 kHz by the cry computer. For each cry utterance (defined as a cry during the expiratory phase of respiration lasting at least 0.5 seconds), we

used the Fast Fourier Transform to compute the log magnitude spectrum for each 25-ms block of the cry utterance. The following 14 cry variables were analyzed based on previous work^{38,39,41}: threshold (number of stimuli to elicit a cry) latency (interval in seconds, stimulus to cry onset), number of utterances, number of short utterances (<0.5 seconds), duration (seconds) of first cry utterance, duration (seconds) of second cry utterance, inspiratory period (interval in seconds between first and second cry utterance), dysphonation (percentage of 25-ms blocks with a low signal to noise ratio, ie, aperiodic sound), number of mode changes (between phonation and dysphonation), energy (dB level), fundamental frequency (Hz, voice pitch), hyperphonation (percentage of 25-ms blocks with fundamental frequency >1000 Hz), and first and second formants (Hz, resonance frequencies).

Statistical Analysis

Analysis of variance (ANOVA) and χ^2 were used to compare the cocaine-exposed and comparison groups on medical and maternal characteristics. The dependent neurobehavioral measures were tested with 4 sets of analyses. Analysis 1 is a 2-way ANOVA that tests 2 factors: cocaine exposure (exposed/not exposed) and opiate exposure (exposed/not exposed). The ANOVA (type 3 sum of squares) tests each factor after adjustment for the other. Analysis 2 is a 2-way ANOVA that tests cocaine and opiate effects after controlling for the standard covariate set described below. Analysis 3 is a univariate analysis of heavy, some, and no cocaine use. Heavy cocaine use was defined as ≥ 3 days per week during the first trimester similar to criteria used by others.²⁰ Any other cocaine use was considered some use. For this analysis, subjects ($n = 91$) were excluded when there was any opiate use during pregnancy based on initial hospital interview, toxicology, or self-report on the MISU. Opiate use was excluded because opiate use could co-occur with heavy, some, or no cocaine use and potentially confound level of cocaine exposure effects. Thus, the sample for the third analysis consisted of 1032 subjects. Analysis 4 is a 1-way ANOVA that contrasts the 3 quantity of cocaine use groups after controlling for the standard covariate set described below.

Standard Covariate Set

Analyses 2 and 4 included covariates selected either for conceptual reasons or because they met the following statistical criteria: the variable is correlated with both drug exposure and NNNS or cry outcome ($p < .05$) and not highly correlated with other covariates (Pearson $r < 0.70$).^{12,42–44} Variables in Tables 1 and 2 were examined for possible inclusion as covariates. The covariates that were used in the adjusted analysis included 11 variables that controlled for the Index of Social Position Score from the Hollingshead scale (socioeconomic status [SES]), birth weight, a birth weight by cocaine interaction term, and site (not interpreted in this study) and 7 polydrug use variables. The extent and kind of drug use reported in the MISU was used to generate polydrug covariates for alcohol, marijuana, and tobacco by averaging reported use across the 3 trimesters of pregnancy. Because all of the drug variables had nonnormal distributions, each was reduced to 3 categories of use (heavy, some, and no use). Cutoffs were based on thresholds for detecting effects that have been reported by others.^{45–50} For alcohol, heavy use was ≥ 0.5 oz of absolute alcohol per day (1 standard drink). For marijuana, heavy use was defined as ≥ 0.5 joints per day. For tobacco, heavy use was defined as ≥ 10 cigarettes per day. Each 3-category drug variable was then used to construct 2 effect codes that served as planned

TABLE 1. Medical Characteristics of Cocaine- or Opiate-Exposed and Comparison Groups

	Cocaine-Exposed			Opiate-Exposed		
	Yes (N = 600)	No (N = 788)	P	Yes (N = 115)	No (N = 1273)	P
Best obstetric gestational age (wk)	36.07 (4.02)	36.39 (4.02)	.142	36.58 (4.08)	36.23 (4.02)	.369
Birth weight (g)	2544 (749)	2695 (862)	.001	2619 (847)	2631 (816)	.888
Length (cm)	46.26 (4.75)	47.11 (5.18)	.002	46.47 (5.32)	46.77 (4.99)	.538
Head circumference (cm)	32.91 (2.89)	32.27 (3.12)	.026	32.05 (3.24)	32.12 (3.01)	.801
Apgar 1 (median)	8	8	.405	8	8	.055
Apgar 5 (median)	9	9	.227	9	9	.446
Male (%)	306 (51.0%)	421 (53.4%)	.370	54 (47.0%)	673 (52.9%)	.224

TABLE 2. Maternal Characteristics of Cocaine- or Opiate-Exposed and Comparison Groups

	Cocaine-Exposed			Opiate-Exposed		
	Yes (N = 600; %)	No (N = 788; %)	P	Yes (N = 115; %)	No (N = 1273; %)	P
Race						
Black	77.8	75.9	.828	50.4	79.1	.000
White	14.7	16.5		40.9	13.5	
Hispanic	6.4	6.4		6.1	6.4	
Other (non-Hispanic)	1.2	1.3		2.6	1.1	
Age						
18–25	20.1	51.1	.000	24.3	38.9	.000
26–35	66.4	40.5		49.6	51.9	
36–49	13.5	8.4		26.1	9.2	
Marital status						
Married	10.6	25.7	.000	17.5	19.3	.164
Never married	85.3	71.8		76.3	77.8	
Divorced/widowed	4.2	2.4		6.1	2.9	
Insurance						
Medicaid	89.1	77.4	.000	82.6	82.4	.494
Self-pay	5.7	3.9		2.6	4.9	
Private/HMO	4.5	18.3		14.8	12.1	
Unknown	.7	.4		0	.6	
Education						
<12 y	49.7	31.5	.000	39.8	39.3	.480
12 y	34.3	43.8		35.4	40.1	
≥13 y	15.9	24.7		24.8	20.6	
Prenatal care (any)	77.4	95.8	.000	85.2	88.1	.363

HMO indicates health maintenance organization.

comparisons (orthogonal contrasts). One effect code contrasted heavy use versus some and no use. The second effect code contrasted some use versus no use. When the no use versus some use comparison is statistically significant and the high versus no/some use comparison is not significant, the interpretation is that there is no additional effect of the higher use group. That is, the threshold for the effect is at the cutoff for the low use group. In addition, a separate indicator variable (yes/no) for binge drinking was defined as >5 drinks at 1 time or on any 1 day.

RESULTS

Medical and Maternal Characteristics

Medical characteristics of the infants are presented in Table 1. There were no statistically significant ($P > .05$) differences between the exposed and comparison groups on gestational age, birth weight, length, head circumference, Apgar scores, and gender. Preterm infants (<38 weeks) accounted for 41% ($n = 270$) of the cocaine/opiate-exposed group and 43% ($n = 314$) of the comparison group (not significant). The percentages of preterm infants who were born at <33 weeks was 10.8% ($n = 71$) in the cocaine/opiate-exposed group and 12.5% ($n = 91$) in the comparison group (not significant). Demographic information on the mothers is presented in Table 2. Mothers in the cocaine/opiate-exposed group were more likely to be older, not married, on Medicaid and not private insurance, less educated, and less likely to receive prenatal care than mothers in the comparison group.

Maternal Drug Use

On the basis of the hospital interview, more mothers in the exposed group used alcohol during pregnancy ($n = 461$ [70.3%]) than in the comparison group ($n = 361$ [49.5%]; $P < .001$). Similarly, more mothers in the exposed group used tobacco ($n = 535$ [81.6%]) than in the comparison group ($n = 211$ [28.9%]; $P < .001$), and more mothers in the exposed group used marijuana ($n = 253$ [38.6%]) than in the

comparison group ($n = 71$ [9.7%]; $P < .001$). On the basis of the MISU interview, Table 3 describes patterns of cocaine use for admitted users. As expected, cocaine use declined during the 3 trimesters. For example, the percentage of women who reported daily use decreased from 17% in the first trimester to 7% in the third trimester with a corresponding increase in the percentage of women who were not using, from 16% in the first trimester to 33% in the third trimester. The 117 (33.2%) women who used cocaine ≥3 days per week during the first trimester compose the heavy use group in the study.

The results of the categorization of the drug covariates showed 15.4% heavy alcohol use, 48.4% some alcohol use, 36.1% no alcohol use, and 21.1% binge. For marijuana, there was 6.9% heavy use, 21.9% some use, and 71.2% no use. For tobacco, there was 23.6% heavy use, 30.9% some use, and 45.5% no use. Opiate use occurred in 4.9% of the sample.

Neurodevelopmental Outcome on the NNNS

Results of analysis of NNNS measures (Tables 4 and 5) are presented as unadjusted before covariates were used and adjusted with covariates included. The adjusted means are shown in the tables.

TABLE 3. Patterns of Cocaine Use for Admitted Users

Cocaine Use	Trimester					
	First		Second		Third	
	N	(%)	N	(%)	N	(%)
Daily	61	(17.3)	40	(11.3)	25	(7.2)
3–6 d/wk	56	(15.9)	45	(12.7)	32	(9.2)
1–2 d/wk	93	(26.3)	77	(21.8)	62	(17.8)
1–3 d/mo	57	(16.1)	68	(19.3)	55	(15.8)
1–2 d 3 mo	28	(7.9)	30	(8.5)	58	(16.6)
Not at all	58	(16.4)	93	(26.3)	117	(33.5)

TABLE 4. NNNs Scales in Cocaine- and Opiate-Exposed and -Nonexposed Infants

Measure	Prenatal Cocaine-Exposed						Prenatal Opiate-Exposed					
	Yes			No			Yes			No		
	N	Mean \pm SE	Adjusted	N	Mean \pm SE	Adjusted	N	Mean \pm SE	Adjusted	N	Mean \pm SE	Adjusted
Attention	423	5.42 \pm 0.10	.313	686	5.34 \pm 0.09	.748	86	5.42 \pm 0.15	.035	1023	5.33 \pm 0.05	.536
Arousal	457	4.37 \pm 0.05	.341	741	4.44 \pm 0.05	.480	91	4.42 \pm 0.08	.747	1107	4.40 \pm 0.02	.789
Regulation*	450	4.91 \pm 0.06	.480	732	4.93 \pm 0.06	.407	91	4.86 \pm 0.10	.076	1091	4.98 \pm 0.03	.224
Handling	430	0.55 \pm 0.02	.124	713	0.56 \pm 0.02	.044	87	0.56 \pm 0.03	.304	1056	0.55 \pm 0.01	.930
Quality of movement	455	4.43 \pm 0.06	.208	740	4.49 \pm 0.05	.369	91	4.49 \pm 0.08	.917	1104	4.43 \pm 0.03	.467
Excitability*	460	4.12 \pm 0.17	.032	751	4.03 \pm 0.15	.167	91	4.16 \pm 0.25	.064	1120	3.99 \pm 0.08	.506
Lethargy	460	3.37 \pm 0.16	.688	751	3.31 \pm 0.14	.735	91	3.28 \pm 0.24	.098	1120	3.41 \pm 0.07	.589
Nonoptimal reflexes	460	4.48 \pm 0.16	.410	751	4.37 \pm 0.14	.542	91	4.54 \pm 0.24	.800	1120	4.31 \pm 0.08	.352
Asymmetrical reflexes	460	1.00 \pm 0.08	.501	751	0.90 \pm 0.07	.520	91	0.93 \pm 0.12	.905	1120	0.97 \pm 0.04	.730
Hypertonicity	460	0.53 \pm 0.06	.542	746	0.63 \pm 0.06	.501	91	0.55 \pm 0.03	.862	1115	0.56 \pm 0.10	.852
Hypotonicity	460	0.18 \pm 0.04	.501	746	0.20 \pm 0.04	.501	91	0.20 \pm 0.06	.800	1115	0.19 \pm 0.02	.852
Stress/abstinence	460	0.18 \pm 0.01	.501	751	0.18 \pm 0.01	.520	91	0.19 \pm 0.01	.001	1120	0.17 \pm 0.01	.195

SE indicates standard error.

* Significant cocaine by birth weight interaction (reported in text).

Cocaine and Opiate Effects

With no adjustment for covariates, cocaine-exposed infants showed poorer quality of movement than infants who were not exposed to cocaine (Table 4, unadjusted). With adjustment for covariates, cocaine-exposed infants showed lower arousal, lower regulation, and higher excitability than infants who were not exposed to cocaine (Table 4, adjusted). Opiate-exposed infants showed higher orientation scores and more stress abstinence signs than infants who were not exposed to opiates with no adjustment for covariates (Table 4, unadjusted). With adjustment for covariates, there were no significant opiate effects.

Covariate Effects for Cocaine and Opiate Exposure

Significant cocaine by birth weight interactions indicated that the infants with poorer regulation ($P = .032$) and higher excitability ($P = .014$) were cocaine exposed or they were low birth weight but not cocaine exposed. Lower birth weight infants also had a poorer quality of movement ($P < .001$), more signs of stress/abstinence ($P < .001$), more hypertonia ($P < .001$), and a greater number of nonoptimal reflexes ($P = .020$). Other covariate effects included lower orientation scores for infants in the binge-drinking group ($P = .020$) and more stress abstinence signs in the some compared with the no marijuana use group ($P = .030$).

Level of Cocaine Exposure

The analysis for heavy, some, and no cocaine exposure with no adjustment for covariates showed more hypertonicity in the heavy cocaine-exposed group (Table 5, unadjusted). With adjustment for covariates (Table 5, adjusted), infants with some cocaine exposure were less aroused than infants with no cocaine exposure, and infants with heavy cocaine exposure showed poorer regulation, higher excitability, and more nonoptimal reflexes than infants with some or no cocaine exposure.

Covariate Effects for Level of Cocaine Exposure

The interaction of birth weight by level of cocaine showed poorer regulation ($P = .018$) and higher excitability ($P = .040$) in lower birth weight, unexposed infants and in both the heavy and some exposed groups. Lower birth weight was related to a greater number of nonoptimal reflexes ($P = .011$), more stress/abstinence signs ($P = .021$), poorer quality of movement ($P = .049$), and more hypertonia ($P = .018$). Higher excitability scores were found in the heavy marijuana use group compared with the some and no marijuana use groups ($P = .043$).

Neurodevelopmental Outcome on Cry

Results of analysis of cry measures (Tables 6 and 7) are presented as unadjusted before covariates were used and adjusted with covariates included. The adjusted means are shown in the tables.

Cocaine and Opiate Effects

With no adjustment for covariates, the cry of cocaine-exposed infants had more energy, a higher fun-

TABLE 5. NNNS Scores in Heavy, Some, and No Cocaine Exposure Groups

Measure	Cocaine Exposure							
	Heavy		Some		None		<i>P</i>	
	<i>N</i>	Mean \pm SE	<i>N</i>	Mean \pm SE	<i>N</i>	Mean \pm SE	Unadjusted	Adjusted
Attention	101	5.42 \pm 0.15	209	5.36 \pm 0.11	632	5.29 \pm 0.07	.821	.293
Arousal	111	4.37 \pm 0.07	226	4.28 \pm 0.05	684	4.43 \pm 0.03	.082	.029
Regulation*	107	4.95 \pm 0.10	225	5.00 \pm 0.07	675	5.00 \pm 0.04	.798	.024
Handling	101	0.51 \pm 0.03	215	0.56 \pm 0.02	658	0.56 \pm 0.01	.257	.121
Quality of movement	110	4.40 \pm 0.08	226	4.41 \pm 0.06	683	4.46 \pm 0.04	.444	.147
Excitability*	111	4.01 \pm 0.24	227	3.89 \pm 0.18	694	3.96 \pm 0.11	.717	.044
Lethargy	111	3.47 \pm 0.23	227	3.49 \pm 0.17	694	3.39 \pm 0.10	.088	.105
Nonoptimal reflexes	111	4.89 \pm 0.23	227	4.21 \pm 0.17	694	4.27 \pm 0.10	.076	.039
Asymmetrical reflexes	111	1.04 \pm 0.11	227	0.93 \pm 0.08	694	0.95 \pm 0.05	.796	.600
Hypertonicity	111	0.67 \pm 0.09	227	0.45 \pm 0.07	689	0.52 \pm 0.04	.042	.062
Hypotonicity	111	0.26 \pm 0.06	227	0.16 \pm 0.04	689	0.20 \pm 0.03	.289	.966
Stress/abstinence	111	0.18 \pm 0.01	227	0.17 \pm 0.01	694	0.17 \pm 0.01	.923	.591

SE indicates standard error.

* Significant cocaine by birth weight interaction (reported in text).

damental frequency, and a lower second formant than the cry of infants who were not exposed to cocaine (Table 6, unadjusted). There were no effects on cry with adjustment for covariates. With no adjustment for covariates, opiate-exposed infants had fewer short utterances than infants who were not exposed to opiates (Table 6, unadjusted). With adjustment for covariates, the effects of opiate exposure on short utterances remained, and there was more hyperphonation in opiate-exposed than in infants who were not exposed to opiates (Table 6, adjusted). There were also significant cocaine by opiate interactions on energy and fundamental frequency with the highest energy ($P = .023$) and fundamental frequency ($P = .020$) in infants who were exposed to both cocaine and opiates.

Covariate Effects for Cocaine and Opiate Exposure

Low birth weight was correlated with fewer utterances ($P = .001$), fewer short utterances ($P = .001$), less energy ($P = .002$), and a higher second formant ($P < .001$). Infants in the some alcohol use group had a lower cry threshold than infants in the no alcohol use group ($P = .011$). Infants in the high marijuana use group showed more mode changes ($P = .019$) and a higher second formant ($P = .019$) than infants in the some and no marijuana use groups.

Level of Cocaine Exposure

With no adjustment for covariates, there was more dysphonation in the cries of infants with heavy cocaine exposure than in the cries of infants with some or no cocaine exposure (Table 7, unadjusted). With adjustment for covariates, the duration of the second cry utterance was longer in heavy compared with some or no cocaine exposure (Table 7, adjusted).

Covariate Effects for Level of Cocaine Exposure

The birth weight by level of exposure interaction showed that the infants in the low birth weight, heavy exposure group had longer second duration utterances than the other groups ($P = .043$). Lower birth weight was associated with fewer cry utterances ($P = .019$), fewer short utterances ($P = .002$), shorter latency ($P = .021$), less energy ($P = .001$), a

higher second formant ($P = .002$), and a longer duration of the second cry utterance ($P = .023$). Infants in the some alcohol use group showed a lower cry threshold than infants in the no alcohol use group ($P = .026$). Infants in the high alcohol use group showed a higher proportion of hyperphonation ($P = .040$). Infants in the binge group had a lower first formant ($P = .033$). Infants in the some alcohol use group had a lower cry threshold than infants in the no alcohol use group ($P = .038$). Infants in the high marijuana use group showed more mode changes ($P = .010$) and a higher second formant ($P = .005$) than infants in the no and some marijuana use groups.

Additional Covariate Effects

SES and site were included as covariates in all of the analyses reported above. Therefore, the exposure effects reported above were not attributable to SES or site differences. However, for reporting purposes, we note that there were only 6 SES covariate effects out of the 74 analyses. However, site effects were observed 72 times. We did test the exposure status by site interaction term for each dependent variable to determine whether we needed to explore further the site effects. However, none of the interaction terms was statistically significant.

We also repeated the analyses with covariates (analysis 2 and 4) excluding birth weight and the birth weight by cocaine interaction from the list of covariates because it has been argued that if cocaine affects birth weight, then the inclusion of birth weight as a covariate will mask the effects of cocaine.²⁰ Results showed that for the NNNS, the exclusion of birth weight and the interaction term as covariates did not result in additional statistically significant effects in analysis 2 or 4. In fact, all 3 effects in analysis 2 and 2 of 4 effects in analysis 4 were no longer statistically significant with these terms excluded. For cry, 2 effects were observed in analysis 1 (unadjusted for covariates) that were observed when birth weight and the interaction term were excluded in analysis 2. However, in analysis 4, there were no statistically significant effects when these covariates were excluded.

TABLE 6. Cry Variables in Cocaine- and Opiate-Exposed and -Nonexposed Infants

Measure	Prenatal Cocaine-Exposed						Prenatal Opiate-Exposed					
	Yes			No			Yes			No		
	N	Mean \pm SE	Adjusted	N	Mean \pm SE	Adjusted	N	Mean \pm SE	Adjusted	N	Mean \pm SE	Adjusted
Threshold (n)	352	1.97 \pm 0.02	.065	544	1.96 \pm 0.01	.236	63	1.97 \pm 0.02	.236	833	1.96 \pm 0.01	.869
Latency (sec)	352	2.50 \pm 0.27	.962	547	2.47 \pm 0.25	.546	64	2.28 \pm 0.41	.546	835	2.70 \pm 0.14	.495
Utterances (n)	352	11.77 \pm 0.53	.170	547	11.11 \pm 0.49	.598	64	11.31 \pm 0.81	.598	835	11.57 \pm 0.27	.389
Short utterances (n)	352	15.07 \pm 0.77	.435	547	15.06 \pm 0.72	.483	64	13.89 \pm 1.18	.483	835	16.24 \pm 0.39	.027
Duration first utterance (sec)	352	2.23 \pm 0.14	.512	547	2.16 \pm 0.13	.364	64	2.11 \pm 0.21	.364	835	2.29 \pm 0.07	.306
Duration second utterance (sec)	344	1.42 \pm 0.07	.826	525	1.46 \pm 0.07	.364	62	1.43 \pm 0.11	.364	807	1.45 \pm 0.04	.943
Inspiratory period (sec)	344	2.58 \pm 0.25	.753	525	2.50 \pm 0.24	.111	62	2.24 \pm 0.39	.111	807	2.79 \pm 0.13	.363
Dysphonation (%)	352	12.82 \pm 1.24	.329	547	13.03 \pm 1.14	.480	64	14.30 \pm 1.89	.480	835	11.55 \pm 0.62	.066
Mode changes (n)	352	2.45 \pm 0.18	.131	547	2.71 \pm 0.18	.437	64	2.84 \pm 0.30	.437	835	2.32 \pm 0.10	.102
Energy (dB)*	352	42.25 \pm 0.74	.016	547	34.65 \pm 2.12	.919	64	39.40 \pm 1.6	.919	835	37.51 \pm 2.1	.973
Fundamental frequency (Hz)*	351	479.53 \pm 8.86	.037	545	453.31 \pm 7.90	.594	63	463.78 \pm 11.08	.594	833	470.05 \pm 3.64	.582
Hyperphonation (%)	352	2.90 \pm 0.71	.329	547	3.46 \pm 0.66	.140	64	4.29 \pm 1.08	.140	835	2.07 \pm 0.36	.066
First formant (Hz)	351	1640.69 \pm 29.47	.174	545	1615.67 \pm 27.26	.539	63	1614.36 \pm 44.91	.539	833	1642.00 \pm 14.79	.812
Second formant (Hz)	351	3950.86 \pm 29.74	.046	545	3959.86 \pm 27.51	.690	63	3973.51 \pm 45.32	.690	833	3937.21 \pm 14.93	.919

SE indicates standard error.

* Significant cocaine by opiate interaction for analyses with and without covariates (reported in text).

DISCUSSION

This is the largest prospective study reported on the effects of prenatal cocaine/opiate exposure on neurobehavioral outcome in early infancy. It is the first such study to combine the detection of prenatal drug exposure with the meconium assay, use a neurobehavioral battery designed to be sensitive to drug effects, and study threshold effects not only for cocaine but also for drug covariates (alcohol, tobacco, and marijuana). Our findings add to the increasing corpus of literature showing that the effects of cocaine are subtle. Furthermore, we show that these subtle effects can be detected when studied in the context of threshold effects for cocaine and other drugs and that NNNS and cry reveal complimentary effects of prenatal drug exposure.

NNNS

We found effects of cocaine exposure and level of cocaine exposure on infant neurobehavior using the NNNS, especially with adjustment for covariates. It has been suggested³⁹ that there are distinct neurobehavioral profiles of cocaine-exposed infants with some highly aroused (excitable) and others more lethargic (depressed). In studies using the NBAS, cocaine effects have been related to the organization of state behavior, including higher excitability²¹ and depression²² scores, lower state regulation and inability to remain alert,¹⁹ and lower arousal.⁵¹ Effects of heavy cocaine exposure have also been reported on the NBAS.^{21,52} In previous work with the NNNS at birth, we also found evidence for depressed and excitable behavior related to prenatal cocaine exposure.³² Our findings of lower arousal and higher excitability further support the construct of excitable and depressed neurobehavioral patterns in cocaine-exposed infants. Both result in poor self-regulation, which may provide a unifying construct.

We also found that poor regulation and higher excitability was attributable to heavy cocaine exposure and that the lowest arousal scores were in the some cocaine exposure but not in the heavy cocaine exposure group, suggesting that specific neurobehavioral syndromes may be related to level of exposure status. Higher doses of cocaine may produce excitable infants, whereas lower doses of cocaine may produce lethargic infants.

Neurobehavioral effects may also be related to low birth weight. Scafaldi et al⁵³ reported poorer state regulation, lower range of state, and higher depression in cocaine-exposed preterm infants than in unexposed preterm infants. We also found low birth weight related to poorer regulation, higher excitability, poor movement, more stress abstinence signs, hypertonia, and nonoptimal reflexes consistent with other findings.⁵⁴ Thus, the neurobehavioral profile of the cocaine-exposed infant may be determined, at least in part, by birth weight and level of cocaine exposure.

We found no stress/abstinence effects attributable to cocaine exposure. Eisen et al⁵⁵ did report more stress behaviors in cocaine-exposed infants. We found more stress/abstinence signs in the opiate-

TABLE 7. Cry Variables in Heavy, Some, and No Cocaine Exposure Groups

Measure	Cocaine Exposure							
	Heavy		Some		None		<i>P</i>	
	<i>N</i>	Mean \pm SE	<i>N</i>	Mean \pm SE	<i>N</i>	Mean \pm SE	Unadjusted	Adjusted
Threshold	89	1.94 \pm 0.02	166	1.97 \pm 0.02	506	1.95 \pm 0.01	.221	.131
Latency (sec)	89	2.48 \pm 0.39	166	2.93 \pm 0.29	508	2.76 \pm 0.19	.837	.084
Utterances (<i>n</i>)	89	10.58 \pm 0.76	166	12.30 \pm 0.57	508	11.21 \pm 0.36	.285	.511
Short utterances (<i>n</i>)	89	15.85 \pm 1.16	166	16.18 \pm 0.84	508	15.92 \pm 0.53	.676	.361
Duration first utterance (sec)	89	2.31 \pm 0.20	166	2.31 \pm 0.15	508	2.25 \pm 0.10	.833	.350
Duration second utterance (sec)*	86	1.56 \pm 0.10	161	1.42 \pm 0.08	488	1.47 \pm 0.05	.426	.046
Inspiratory period (sec)	86	2.79 \pm 0.36	161	2.87 \pm 0.28	488	2.73 \pm 0.18	.936	.089
Dysphonation (%)	89	14.60 \pm 1.74	166	10.46 \pm 1.32	508	11.86 \pm 0.85	.050	.105
Mode changes (<i>n</i>)	89	2.49 \pm 0.28	166	2.05 \pm 0.21	508	2.46 \pm 0.13	.086	.938
Energy (dB)	89	3733.97 \pm 274.43	166	3745.75 \pm 206.00	508	3673.04 \pm 131.04	.679	.162
Fundamental frequency (Hz)	89	461.74 \pm 10.50	166	473.04 \pm 7.89	506	471.88 \pm 5.03	.506	.278
Hyperphonation (%)	89	1.42 \pm 0.98	166	1.72 \pm 0.74	508	2.27 \pm 0.47	.719	.172
First formant (Hz)	89	1682.16 \pm 41.05	166	1640.75 \pm 30.84	506	1632.06 \pm 19.69	.326	.657
Second formant (Hz)	89	3960.62 \pm 42.10	166	3916.03 \pm 31.63	506	3938.95 \pm 20.19	.217	.465

SE indicates standard error.

* Significant cocaine by birth weight interaction (reported in text).

exposed group, and other studies have also reported opiate effects on the NBAS.^{56–60} We also found more stress/abstinence signs in the some marijuana use group and higher excitability scores in the heavy marijuana use group. Marijuana effects have also been reported on the NBAS⁶¹ but not using thresholds as in the present study. The finding of stress/abstinence effects in infants who were exposed to opiates and marijuana confirms the sensitivity of the NNNs to measure these effects and supports the null finding of no stress/abstinence effects in the cocaine-exposed infants.

Our finding that opiate-exposed infants had better orientation scores was not found with adjustment for covariates, suggesting that this may not be an opiate effect. There was also a covariate effect showing that lower orientation scores were attributable to binge drinking. Effects of prenatal alcohol exposure have been reported on the NBAS^{61–65} using estimates that measure regular drinking but at higher levels (averages of 1.7–2.32 oz of absolute alcohol per day) than in the present study. These studies did not use a binge variable that may prove useful in future studies in which the average drinking is at lower levels. Note also that the infants in our study were tested at 1 month of age. A few studies used repeated tests during the first month and found stronger effects of cocaine as infants approached 1 month,^{21,66,67} suggesting that the effects of cocaine and other drugs may be more easily detected after the immediate newborn period.

Cry

In previous work, acoustical analysis of cry has been related to prenatal cocaine exposure,^{38,39} opiates,^{68,69} marijuana,⁴⁰ tobacco,⁴¹ and alcohol.^{41,70} Measures of cry acoustics reflect mechanisms that mediate cry production, including central nervous system reactivity (threshold, latency), respiratory control (energy, dysphonation, and utterances), and sound characteristics related to neural control of the vocal tract (fundamental frequency, hyperphonation, formant frequencies, and mode changes).

We found a louder cry (more energy), a higher pitched cry (fundamental frequency), with less resonance in the upper vocal tract (second formant) in cocaine-exposed infants and more turbulence or noise (dysphonation) in the cry signal with heavy cocaine exposure. However, these effects were not observed when adjusted for covariates, suggesting that they are not attributable only to cocaine. The second cry utterance was longer in the heavy cocaine use group with adjustment for covariates. The opiate effects on cry were more short utterances and more hyperphonation (very high pitch, >1000 Hz), and these were maintained with adjustment for covariates. Infants who were exposed to both cocaine and opiates had the loudest and highest pitched cries.

We also found effects of other drugs on cry acoustics. Infants in the some alcohol use group were more reactive, requiring fewer stimuli to elicit the cry (lower threshold), than infants with no alcohol exposure. There was more hyperphonation in the high alcohol use group and a lower first formant in the binge alcohol group. Infants in the high marijuana use group had more glottal instability (mode changes) and a higher second formant.

These findings demonstrate general effects of prenatal drug exposure on the reactivity, respiratory, and neural control components of the cry. In addition, there may be more specific effects that could help identify subgroups of infants at greater risk. For example, high-pitched and hyperphonated cries have been reported in infants with neurologic involvement.⁷¹ This could suggest that the opiate, cocaine plus opiate, and high alcohol use groups are at higher neurologic risk than other infants in our study. Finally, we found, as have others,^{70,71} effects of birth weight on cry. Most of the birth weight effects that we observed were related to the respiratory control aspect of cry production (utterance measures and energy).

General Issues

The statistical power of this sample coupled with sensitive neurobehavioral measures enabled us to

detect drug effects that were not previously possible. Dividing the cocaine sample into heavy versus some use improved the detection of cocaine effects by showing that some effects were attributable only to heavy cocaine exposure. The use of cut points to identify thresholds for drug covariates also improved detection by showing some effects at lower thresholds and some effects only at higher thresholds. These findings underscore the importance of using multiple, neurobehavioral measures to help identify subgroups of infants who are at greater risk and for studying neurobehavioral effects in the context of polydrug use. Our analysis for heavy use was based on a postnatal self-report measure. Postnatal self-report measures of maternal cocaine use has been found to be as effective as antenatal measures in predicting neurobehavioral outcome.⁴⁵ It also avoids the limitations of antenatal measures that rely on clinic-based samples that may limit generalizability. It is also interesting that in the context of polydrug use, we found no evidence of cigarette smoking on NNNS or cry. Other studies have reported effects of cigarette smoking^{41,61,72,73} but not in the context of illegal and polydrug use.

Role of Birth Weight

Context also needs to include low birth weight. We found independent effects of birth weight on NNNS and cry as well as cocaine by birth weight interactions. Birth weight is probably a moderator variable, meaning that effects of cocaine may be different in low birth weight infants than in normal birth weight infants.⁷⁴ We also tested the hypothesis that cocaine effects could be masked by the inclusion of birth weight and the cocaine by birth weight interaction. We found more evidence that the effects of cocaine on NNNS and cry are more visible when these variables were used as covariates than when they were not. We suggest that the use of these factors as covariates controls error variance that serves to unmask further the effects of cocaine on behavior.

Understanding Subtle Effects

The effects reported here are small in magnitude. We did not adjust for multiple comparisons. Adjustment for multiple comparisons protects against rejecting the null hypotheses when it is correct (type I error). However, as suggested by Rothman,⁷⁵ the cost of this protection is to increase the type II error that findings are attributable to chance when they are not. Minimizing type II error or maximizing sensitivity to find effects is especially critical in studies such as ours in which effects are subtle and could easily be missed. It is important that we understand the implications of these subtle effects because they can affect not only our scientific understanding but also public policy and treatment. We found reliable but small differences attributable to drugs that are not necessarily deficits. Although our findings do not provide evidence of a clinically significant disorder or disease process, they do have both short-term and long-term implications.

The short-term importance of these differences is that they reflect neurobehavioral vulnerability that

may be exacerbated by the caregiving environment. Many drug-exposed infants grow up in nonoptimal environments. Therefore, what start out as small differences can become exaggerated and develop into deficits. Our findings suggest certain neurobehavioral characteristics that could provide markers for later deficits, such as poor self-regulation, in cocaine-exposed infants, and the high pitched, hyperphoned cries in cocaine/opiate- and alcohol-exposed infants. Clinically, the drug-exposed infant is probably best thought of as an infant "at risk" rather than as an infant with a known disorder. In addition, environmental risk may interact with neurobehavioral risk. We might expect the lethargic infant to be more at risk for neglect and the excitable infant to be more at risk for abuse. This is said with 2 caveats. The first is the understanding that the concept of "at risk" is vague. Second, our findings are limited to the population studied and may not represent all drug-exposed infants. Most of the pregnant women who use cocaine and most of the subjects in research studies, including ours, are referred to as "recreational users" rather than "hard-core addicts." Even our "heavy users" were rarely daily users, and heavy use was limited to the first trimester only as cocaine use declined throughout pregnancy. The clinical implications of considering these infants as "at risk" infants are that with intervention, later deficits can be prevented.

The long-term implications of these findings are that cocaine may affect areas of the brain that are not manifest until these children reach school. For example, in adult cocaine users, problems with executive function (decision making, judgment, attention, planning, and mental flexibility) are the most frequently reported cognitive deficits.^{76,77} The site of action for cocaine in the brain involves several brain areas that are thought to subserve these functions, including the nucleus accumbens/subcallosal cortex, prefrontal cortex, and limbic prefrontal cortex including the anterior cingulate. Functional magnetic resonance imaging studies and other imaging techniques show response to cocaine infusion in these locations as well as associated areas, including the basal ganglia and parietal cortex. Cocaine may have latent effects that are not yet observed in infancy. It may be that cocaine affects areas of the brain that we cannot evaluate in infancy or that are not manifested until children are older, such as executive function. There are many examples of problems that are undetected in early infancy (attention-deficit/hyperactivity disorder, autism, schizophrenia) that could provide alternative models for understanding prenatal exposure effects. Therefore, it is imperative that these children continue to be followed and that public policy allow for the possibility that even subtle findings in infancy may be a harbinger of more serious long-term deficits.

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THROWING MONEY AT HEALTH SERVICES WILL MEAN MORE TESTS AND TREATMENTS, BUT IT WON'T NECESSARILY PROLONG PEOPLE'S LIVES, WARNS JOHN E. WENNBERG

"It is an enduring assumption of modern life that as medical science advances and health care improves, most of us can expect to lead longer and healthier lives. More diagnostic tests, more powerful body and brain scanners, more high-tech treatments, more drugs: surely this is a recipe for longevity. Provided politicians and health insurers pump enough money into our hospitals and clinics, the benefits are bound to flow. However, things are not that simple. My colleagues and I have found that, at least for older and sicker Americans, more health care does not necessarily mean more health. Our studies consistently show that patients in areas where health care spending is high do not have longer life expectancy. At best, it remains the same as in low-spending regions."

Wennberg JE. *New Scientist*. August 17, 2002:26

Note: John E. Wennberg is director of the Center for the Evaluative Clinical Sciences at the Dartmouth Medical School, Lebanon, New Hampshire.

Noted by JFL, MD

The Maternal Lifestyle Study: Effects of Substance Exposure During Pregnancy on Neurodevelopmental Outcome in 1-Month-Old Infants

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